REMARKS

§102(e) Rejections

Claims 1, 3, 7, and 11-22 were rejected under 35 USC §102(e) as anticipated by Bower *et al.*, U.S. Patent No. 6,057,136 ("Bower"). (Paper No. 28 at 2).

For the reasons set forth below, this rejection respectfully is traversed.

Bower discloses genes of the biotin biosynthetic operon of *Bacillus subtilis*, closely related species thereof, and constructions useful for high level production of biotin. (Abstract). In Bower, the enzymatic steps from pimelyl-CoA (PmCoA) to biotin are disclosed. (Col. 1, lines 17-43 and FIG. 1). The step from 7-keto-8-amino pelargonic acid ("KAPA") to 7,8-diamino-pelargonic acid ("DAPA") is disclosed to be mediated by DAPA amino transferase (bioA). (Col. 1, lines 25-26). In FIG. 1, this step is shown to require S-adenosyl methionine (SAM).

In making the rejection of claims 1, 3, 7, 11, and 12, the Examiner asserted that Bower "teach" a method of producing the biotin vitamers biotin and dethiobiotin by culturing strain BI282, which contains BioW, BioA, BioB, and BioD DNA, in a rich medium and isolating the biotin vitamers. (*Id.*). The Examiner further asserted that the Bower medium "***would be expected*** to provide at least 10 mmoles per liter of lysine or a lysine precursor."[1] (*Id.*). The Examiner then concluded that "[a]lthough

[1] We assume that the Examiner intended that the phrase "at least 10 mmole per liter of lysine or a lysine precursor" recited in the Office Action to mean at least 10 mmole of lysine or a lysine precursor per liter of medium. If this is incorrect, it is requested that the Examiner identify on the record what was intended by the phrase "at least 10 mmole per liter of lysine or a lysine precursor."

Bower *et al.* do not teach that strain BI282 comprises a lysine-utilizing DAPA aminotransferase, BI282 comprises DNA encoding a *B. subtilis* DAPA aminotransferase which inherently uses lysine as an amino group donor." (*Id.* at 2-3).

Initially, we note that the rejection relies on a "***would be expected***" standard for rejecting the claims under §102(e). But, as is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). ***Each and every element*** recited in a claim must be found in a single prior art reference and ***arranged as in the claim***. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.,* 221 USPQ 481, 485 (Fed. Cir 1984).

It is respectfully submitted that "would be expected" is not a substitute for identifying each and every element arranged as in the claim. Thus, there is no room under §102(e) for a "would be expected" standard as applied by the Examiner in this Office Action. And, if the rejection intends to rely on inherency by using the "would be expected" phrase, we note as set forth in more detail below, that "would be expected" is also the wrong standard. For these reasons alone, the rejection is insufficient as a matter of law, and should be withdrawn.

Notwithstanding the legally deficient nature of the rejection, we address below certain factual deficiencies, which also render the rejection inadequate. For example, the Examiner acknowledges that Bower does not disclose that BI282 comprises a lysine-utilizing DAPA aminotransferase. (Paper No. 28 at 2-3). The Examiner, however, relies on an inherency theory to conclude that BI282 uses lysine as an amino donor. (*Id.*). As is well settled, to support an anticipation rejection based on

inherency, an examiner must provide factual and technical grounds showing that the inherent feature "necessarily flows" from the cited prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (B.P.A.I. 1990) and *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981) (inherency must flow as a necessary conclusion from the prior art, not simply a possible one.). Here, the rejection simply contends that "BI282 comprises a *B. subtilis* DAPA aminotransferase which inherently uses lysine as an amino group donor," and that the rich medium "would be expected to provide at least 10 mmoles per liter of lysine or a lysine precursor." (Paper No. 28 at 3).

The rejection, however, provides no factual or technical evidence to support these contentions. The rejection provides no evidence that such conclusions "necessarily flow" from Bower. But, such are the kinds of evidence required to support the asserted inherency rejection. Without more, the rejection is factually deficient, and should be withdrawn for this reason also.

Because the rejected claims are ***methods***, to show inherency, the Examiner was required to show ***each and every element*** of the claimed ***method*** literally or inherently. This the rejection has not even attempted to do. For the Examiner's convenience, claim 1 is reproduced below:

> 1. (Amended) A ***method*** of producing a biotin vitamer by:
>
> (a) culturing a bacterium comprising a lysine-utilizing DAPA aminotransferase, said culturing taking place in an environment wherein ***lysine, a lysine analog, or a lysine precursor is exogenously added to the culture*** and ***totals at least 10 mmoles per liter of culture***; and

(b) recovering said biotin vitamer.

Here, the rejection provides no evidence or technical reasoning that Bower discloses literally or inherently "exogenously adding" at least 10 mmols of lysine, a lysine analog, or a lysine precursor per liter of culture to the culture as recited by *e.g.*, claim 1. At most, the rejection contends that the presence of veal infusion broth and yeast extract "***would be expected to provide***" at least 10 mmoles per liter of lysine, a lysine analog, or a lysine precursor. (*Id.* at 2).

That a veal infusion broth and a yeast extract might provide at least 10 mmoles of lysine per liter of culture is simply not enough. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Oelrich*, 212 USPQ at 326. Thus, because the rejection fails to establish that the culture media disclosed in Bower necessarily "provided" at least 10 mmole of lysine, lysine analog, or lysine precursor per liter of culture it fails for this additional reason, and should be withdrawn.

Assuming *arguendo* that veal infusion broth and yeast extract, alone or in combination "provided" at least 10 mmoles of lysine per liter of culture, the rejection presents no evidence or technical reasoning that Bower discloses, literally or inherently, "***exogenously adding***" lysine, a lysine analog, or a lysine precursor to the culture as recited by *e.g.*, claim 1. At most, the rejection asserts that the "medium used comprises veal infusion broth and yeast extract." (Paper No. 28 at 2). Consistent with the rejection's summary of Bower, the Examiner also relies on Table 11 to show the fermentation media used in various experiments. An inspection of Table 11 demonstrates that both veal infusion broth and yeast extract are part of the initial

fermentation batch, *i.e.*, they are combined with the other initial components to make up the initial batch. The rejection identifies no disclosure in Bower whereby veal infusion broth or yeast extract, alone or combined are "exogenously added" to a culture as recited in the claims. For this reason, as well, the rejection should be withdrawn.

With respect to claims 13-19, 21, and 22, the Examiner asserted that Bower "teach" a method of producing the biotin vitamers biotin and dethiobiotin by culturing *E. coli* strain MM294 transformed with plasmid pBIO289, which contains BioW, BioA, BioB, and BioD DNA, in a rich medium and isolating the biotin vitamers. (Paper No. 28 at 3). The Examiner also asserted that a "rich medium ***would be expected to contain*** methionine as well as provide at least 10 mmoles per liter of lysine or a lysine precursor." (*Id.*). The Examiner acknowledged that Bower do not teach that the BioA of pBIO289 encodes a lysine-utilizing DAPA aminotransferase, but summarily concluded that the "encoded *B. subtilis* DAPA aminotransferase would inherently use lysine as an amino group donor." (*Id.*).

For essentially the same reasons as set forth above, this rejection is also, respectfully traversed.

As we noted above, "would be expected" is simply not the standard for a rejection under §102(e) either literally or under the doctrine of inherency. The rejection's unsupported assertion that a rich medium "***would be expected to contain*** methionine as well as to provide 10 mmoles per liter of lysine or a lysine precursor" does not identify by page and line number where such elements of the claimed invention are found. In short, such an assertion fails to meet the statutory requirement of demonstrating the "identity of invention." And, as observed above, "would be

expected" is not equivalent to "necessarily flows," and leaves open too many "possibilities" or "probabilities" to meet the strict inherency standard. In essence, the "would be expected" standard impermissibly removes the Examiner's burden of setting forth a *prima facie* case of anticipation, and unfairly shifts the burden of coming forward with evidence to rebut such a nebulous assertion to the Applicants. But, as is well settled, such burden shifting is erroneous as a matter of law. For this reason alone, the rejection should be withdrawn.

Notwithstanding the legally erroneous nature of the rejection, for completeness, we address below the rejection's factual deficiencies as well.

Because the rejected claims are ***methods***, to set forth a prima facie case of anticipation, the Examiner was required to show each and every step of the claimed ***method*** literally or inherently. The rejection, however, fails to address ***any*** step of the claimed methods, let alone each of the recited steps.

Here, the rejection provides no evidence or technical reasoning that Bower discloses, literally or inherently, "exogenously adding" at least 10 mmols of lysine, a lysine analog, or a lysine precursor per liter of culture to the culture as recited by *e.g.*, claims 1, 17, and 18. At most, the rejection contends that a rich medium "***would be expected*** to contain methionine as well as provide at least 10 mmoles per liter of lysine or a lysine precursor." (Paper No. 28 at 3).

Likewise, the rejection provides no evidence or technical reasoning that Bower discloses, literally or inherently, "adding" SAM or an analog of SAM to the culture as recited by *e.g.*, claim 14. At most, the rejection contends that a rich medium "***would be expected to contain***" methionine. (*Id.*).

That certain types of rich media might "contain" or might "provide" at least 10 mmoles of lysine or SAM per liter of media is simply not good enough. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Oelrich*, 212 USPQ at 326. For this reason, as well, the rejection should be withdrawn.

Assuming *arguendo* that a "rich" media "contains" or "provides" at least 10 mmoles per liter of lysine and SAM, the rejection provides no evidence or technical reasoning that Bower discloses literally or inherently "***exogenously adding***" lysine, a lysine analog, or a lysine precursor to the culture as recited by *e.g.*, claims 1, 17, and 18 or adding methionine, SAM or a SAM analog as recited by *e.g.*, claim 14. At most, the rejection asserts that "a rich medium ***would be expected to contain*** methionine as well as provide at least 10 mmoles per liter of lysine or a lysine precursor." (Paper No. 28 at 3). In short, the rejection fails to identify where in the passages relied upon (*i.e.*, "col., 21, lines 20-56" and "col. 22, Table 5") lysine or SAM is inherently added to the culture medium. Thus, even if lysine and SAM are "provided" by or "contained" in the culture media disclosed by Bower, the rejection is absolutely silent as to the claimed ***step*** of "exogenously adding" lysine or SAM as recited in *e.g.*, claims 1, 14, 17, and 18. For this reason, as well, the rejection should be withdrawn.

§§102(e)/103(a) Rejections

Claims 8 and 20 were rejected as being unpatentable over Bower in view of Yamada *et al.*, U.S. Patent No. 4,563,426 ("Yamada"). (Paper No. 28 at 4-5).

For the reasons set forth below these rejections, respectfully are traversed.

In making the rejection of claim 8, the Examiner relied on Bower as applied to claims 1 and 3 in the present Office Action. (*Id.* at 4). The Examiner acknowledged, however, that Bower "do not teach" converting the recovered dethiobiotin to biotin by an additional fermentation. (*Id.*). To fill this acknowledged gap, the Examiner relied upon Yamada as teaching a method of producing biotin by adding dethiobiotin to a fermentation medium. (*Id.*). The Examiner then contended that it would have been obvious to produce dethiobiotin, as taught by Bower, and to convert the dethiobiotin into biotin as taught by Yamada to produce biotin. (*Id.*).

With respect to claim 20, the Examiner relied on Bower as applied to claim 13 in the present Office Action. (*Id.* at 5). The Examiner acknowledged, however, that Bower "do not teach" converting the recovered dethiobiotin to biotin by an additional fermentation. (*Id.*). To fill this acknowledged gap, the Examiner relied upon Yamada as teaching a method of producing biotin by adding dethiobiotin to a fermentation medium. (*Id.*). The Examiner then contended that it would have been obvious to produce dethiobiotin, as taught by Bower, and to convert the dethiobiotin into biotin as taught by Yamada to produce biotin. (*Id.*).

A continued prosecution application (CPA) is being filed concurrently herewith. In view of this filing, the present application is entitled to use the provisions of 35 USC §103(c) to remove Bower from the present §§102(e)/103(a) rejection. Accordingly, the following statement is presented upon information and belief:

The present application and Bower were, at the time the invention of the present application was made, owned by, or subject to an obligation of assignment to the same company, Roche Vitamins Inc.

The foregoing statement alone is sufficient to remove Bower from the §§102(e)/103(a) rejection. *See* MPEP §706.02(l)(2) at 700-39, 8th Ed. (August 2001). Thus, the primary document relied upon by the Examiner has been removed. In view of the foregoing, the rejection is factually and legally insufficient to support a rejection under §103(a). *In re Rijckaert*, 28 USPQ2d 1955, (Fed. Cir. 1993) (secondary document found insufficient to fill gaps left by primary document). In view of the foregoing, the rejections of claims 8 and 20 under §§102(e)/103(a) have been rendered moot, and should be withdrawn.

In view of the foregoing, favorable action on the merits including withdrawal of the rejections and allowance of all the claims, respectfully, is requested. If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

Respectfully submitted,

By: _____

Kevin C. Hooper
Registration No. 40,402
BRYAN CAVE LLP
245 Park Avenue
New York, NY 10167-0034
(212) 692-1800